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Does craving for cocaine mediate cocaine use? Analysis of a randomised controlled pilot trial of memory-focused cognitive therapy

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ABSTRACT

Cocaine Use Disorder (CUD) is a debilitating psychopathology, with no recommended medication therapy or specific psychological intervention. Memory-focused cognitive therapy (MFCT) is a novel psychotherapy for CUD, theorised to modify and re-consolidate cocaine craving-related memories for cognitive and behavioural control. A pilot randomised controlled trial indicated that this therapy is associated with reduced craving and cocaine use. With an 80% confidence interval set for null hypothesis testing, we conducted an exploratory causal mediation analysis with confounder adjustment to determine if increased cocaine abstinence following MFCT is mediated by reduced craving experience and increased emotion regulation. Participant data on the Difficulties in Emotion Regulation Scale did not meet screening evaluation as a potential mediator. Cocaine craving (assessed by the frequency version of the Craving Experience Questionnaire) was associated with a total treatment effect of MFCT on cocaine abstinence at follow-up (1.499; 80% CI 1.114 to 1.970; $p = 0.012$). A significant natural indirect effect indicated that reductions in cocaine use were strongly mediated by reduced frequency of craving experience (1.753; CI 80% 1.334 to 2.936; $p < 0.0001$). This study provides exploratory evidence in support of the theoretical action for MFCT and underscores the importance of craving as a therapeutic target.

Keywords: cocaine use disorder; craving; memory; reconsolidation; cognitive behavioural therapy; mediation

INTRODUCTION

Cocaine use disorder (CUD; Diagnostic and Statistical Manual [DSM-5]; American Psychiatric Association, 2013) is a debilitating psychopathology. In DSM-5, CUD has 11 symptoms, spanning increased tolerance, withdrawal symptoms, urges to use cocaine (craving) and several behavioural, health and social problems associated with chronic consumption.

Among these symptoms, influential models of addiction position the cognitive-affective construct – craving – in a key disorder maintaining role (Robinson & Berridge, 1993; Tiffany, 1990; West, 2006). Craving is a highly subjective construct. It is clear from patient reports that the content and strength of craving varies widely. An episode can be brief or protracted and distressing. Etiologically, craving can be understood as the product of a drug exposure and associative learning process in which previously drug-neutral situations, objects, people, sensations/moods that present when cocaine is obtained become conditioned stimuli ([CS]; O'Brien, Childress, McLellan, & Ehrman, 1992). An encountered CS (or a direct drug-related cue such as the sight of cocaine or cocaine paraphernalia) can trigger a process of cognitive elaboration in which memory of past drug use – often in the form of a vivid sensory mental image (May et al., 2014; May, Andrade, Panabokke, & Kavanagh, 2004) – induces a desire for pleasure, or the need to alleviate anxiety, stress, or cocaine-related withdrawal symptoms (Baker, Piper, McCarthy, Majeskie, & Fiore, 2004; Koob, Caine, Parsons, Markou, & Weiss, 1997). Negative reinforcement, in particular, can be very strongly motivating for some people with CUD, leading to problems with the regulation of emotion (Cheetham, Allen, Yucel, & Lubman, 2010; Fox, Axelrod, Paliwal, Sleeper, & Sinha, 2007).

In CUD, cocaine-related imagery can drive the maintenance of pro-drug (approach) thoughts, appraisals and dysfunctional beliefs (Andrade, May, & Kavanagh, 2012; Conway, Meares, & Standart, 2004). These cue-induced responses can persist long into abstinence and, if not controlled, can cause relapse (Parvaz, Moeller, & Goldstein, 2016). It is also important to recognise that if a person with CUD has immediate access to cocaine, there may be minimal or no craving-related elaboration (Tiffany, 1990). However, if there is a delay in obtaining cocaine, or there is ambivalence with the desire to be abstinent, craving is likely to be strong, distressing and highly motivating (Kavanagh, Andrade, & May, 2005).

There have been many efforts to develop an effective therapy for CUD. However, to date there are no licensed medications or guideline-recommended specific psychosocial interventions (National Institute for Health and Care Excellence, 2007). Among the latter,

Cognitive Behavioural Therapy (CBT) has been the most widely trialled intervention. A meta-analysis of 53 randomised controlled trials targeting alcohol or another drug disorder calculated that stand-alone CBT is associated with a small overall standardised mean difference for the treatment effect versus control (Hedge's g = 0.154; Magill & Ray, 2009). A more encouraging picture emerged when the authors pooled results from trials that combined CBT with another psychosocial intervention (typically general drug counselling). This strategy was associated with a medium effect size (g = 0.305; $p < 0.005$; 19 trials).

The population of cocaine users is heterogenous. Some powder cocaine users use infrequently, but there is a sub-population who use smokable (crack) cocaine or cocaine powder very intensively and develop CUD; many with considerable unmet treatment need. In England in 2016-2017, it was estimated that there were 760,000 powder cocaine users and 181,000 crack users in the general population (Home Office, 2017; Public Health England, 2017a). In that year, 42,403 people presented to community addiction treatment clinics for help with cocaine-related problems (16,892 powder cocaine and 25,511 crack) of whom 52% had a co-occurring opioid use disorder (Public Health England, 2017b). Community services offer people with CUD general counselling, but many do not engage with this intervention or discontinue treatment after a short time. Among those who are retained in treatment, continued crack cocaine use is a significant predictor of poor response to medication for opioid use disorder (Marsden et al. 2012; Marsden et al. 2019).

Against this background – and encouraged by the potential for a CBT intervention to be effective when offered alongside ongoing general counselling and support – we developed a novel cognitive therapy intervention with the goal of helping people to better recognise, modify and control cocaine craving-related thoughts, emotions and behaviour. Our Memory-Focused Cognitive Therapy (MFCT) is a 15-week, outpatient, individual psychotherapy (Marsden et al., 2017). In addition to a formulation-driven assessment and cognitive restrucuring and behavioural experiments, MFCT adapts to CUD the fear memory reliving, imagery re-scripting and memory reconsolidation paradigm successfully used for the treatment of post-traumatic stress disorder (Brewin, Gregory, Lipton, & Burgess, 2010; Grey, Young, & Holmes, 2002; Holmes & Mathews, 2010). Our MFCT therapy protocol also includes a cue-induction procedure to elicit images and affective responses as therapy targets (Hon, Das, & Kamboj, 2016; Xue et al., 2012).

In psychotherapy, an important part of the evidence-gathering process for a new intervention is to address theoretical hypotheses of how treatment causes change (Kazdin, 2007; Murphy, Cooper, Hollon, & Fairburn, 2009). This is typically done by conducting a causal

mediation analysis (Hayes, 2014; MacKinnon, 2008). A causal mediation analysis tests whether there is evidence that the psychotherapy exposure is related to changes in a hypothesised mediator, and whether the mediator is associated with changes in a subsequent outcome. A randomised controlled trial provides the logical design conditions for causal inference because participants are randomly allocated to the levels of the therapeutic exposure.

Prior to the analysis of the developmental study (Marsden et al., 2018), the statistical analysis plan for the primary and secondary outcome measures was pre-registered (Centre for Open Science; https://www.osf.io/3kfzj/). The results showed that compared to an assessment-only control, the intervention was associated with lower levels of craving (bias corrected Hedge's *g* = -1.62; 95% CI -2.45 to -0.80; the primary outcome measure) and more abstinent days (*g* = 1.19; 90% CI 0.54 to 1.84; the drug use secondary outcome measure). In that report, we stated our plan to determine if craving and emotion regulation mediate cocaine use, thereby giving evidence of the MFCT's theoretical change mechanism.

In this article we present the results of an exploratory causal mediation analysis to estimate the extent to which MFCT is associated with cocaine abstinence through craving experience and emotion regulation. We predict that reduced craving and improved emotion regulation mediates observed treatments effects of MFCT at follow-up.

METHODS

Design, setting and participants

Data for the present study were from a completed and published single-site, 15-week, two-arm, randomised controlled trial contrasting MFCT (the intervention; n=16) to an assessment and cocaine cue-induction only group (the control; n=14).

The published protocol provides a detailed description of the study procedures and interventions (Marsden et al., 2017). Briefly, the intervention comprised 3x90 minute pre-randomisation assessments; 2x30 minute cocaine cue-induction procedures; 5x120 minute individual MFCT sessions over consecutive days; and 3x60 minute MFCT-relapse prevention discussions and research follow-ups at one-week, one-month and three-months conducted as personal interviews at the clinic. The control group received the three-session pre-randomisation assessment, the two cue-induction procedures, and participated in the three research follow-ups only.

The trial was done at an English National Health Service (NHS) community addictions clinic operated by South London and Maudsley Trust and at the National Institute for Health and Research and Wellcome Trust Clinical Research Facility (CRF) at King's College Hospital, London. Ethical approval for the protocol was granted by the UK National Research Ethics Service.

Patients (aged 18 years and over) receiving ongoing general drug counselling were eligible for the trial if they were diagnosed with CUD (Structured Clinical Interview for DSM-5; First, Williams, Karg, & Spitzer, 2015). Study exclusion criteria were current non-abstinent alcohol use disorder[1]; uncontrolled severe mental health disorder; current PTSD[2]; and suicide planning in the past month or a suicide attempt in the past six months. All patients provided their informed written consent.

Measures

The following clinical research measures were used for the analysis (see **Figure 1** for timing during the study):

Difficulties in Emotional Regulation Scale (Gratz & Roemer, 2004). The DERS is a 36-item self-report measure of current emotion regulation. It includes four components: awareness and understanding; acceptance; ability to control impulses in the presence of negative affect; and access to emotion regulation strategies. Items are rated using a five-point scale (almost never to almost always; 0-5; total score: 36-180). Higher scores indicate more difficulty in emotion regulation. Participants completed the DERS at 1-month follow-up and the instrument was screened as a potential mediator for the analysis.

The Craving Experience Questionnaire – frequency version (May et al., 2014). The CEQ-F is an 11-item, self-report measure of the frequency of intensity, imagery and intrusiveness aspects of craving in the past two weeks (adapted for the present study). Each item is rated using an 11-point scale (0-10; total score: 0-110). Participants completed the CEQ-F at baseline and at 1-month follow up and the instrument was screened as a potential mediator for the analysis.

[1] People with non-abstinent alcohol use disorder were judged at risk of presenting to the CRF with intoxication at a level precluding admission (alcohol breath test screening to a maximum of 30 mg/ml).
[2] In the original protocol, we were concerned that a patient with untreated PTSD might not be able to accept or have a negative reaction to a memory relieving procedure, so this exclusion was on safety grounds.

Treatment Outcomes Profile (Marsden et al., 2008). The TOP is a structured, clinician administered interview for substance use disorder treatment outcome research. It includes a calendar prompt, time-line follow-back method to record drug use during the prior 28 days. Participants completed the TOP at baseline and three-month follow-up. The outcome measure for the analysis was the number (count) of days abstinent (NDA) from cocaine at the 3-month follow-up.

Urine Drug Screen (UDS; Alere Toxicology). To indicate recent drug use at the 3-month follow up (and to verify self-report using Cohen's kappa statistic), we used an instant result immunoassay device to detect the primary cocaine metabolite (benzoylecgonine) in urine.

Statistical analysis

Some description is warranted on our conceptual approach for the causal mediation analysis. Rather than follow the traditional method of assessing mediation (Baron & Kenny, 1986), we used the counterfactual framework (Valeri & Vanderweele, 2013; VanderWeele, 2015).

In Baron and Kenny's regression equation approach (see **Figure 2,** panel 1), path c' represents the direct effect of the exposure on the outcome. Path a' estimates the effect of the exposure on the mediator and path b' shows the effect of the mediator on outcome. Taken together, path a' and b' express the indirect effect of the exposure on the outcome via the mediator. This approach has served researchers very well – but it cannot estimate exposure-mediator interactions or handle non-continuous outcome measures (Holland, 1986).

VanderWeele's counterfactual framework was developed to address these limitations (see **Figure 2,** panel 2). Here, the estimation of effects is achieved by comparing observed and hypothetical outcomes for the intervention and control groups, on the assumption of 'exchangeability' (i.e. that people assigned to the control group [A=0] would respond in the same way as people assigned to the intervention group [A*=1] had they been assigned to the intervention, and *vice versa*; (Robins & Greenland, 1992).

A causal mediation model decomposes the total effect (TE) into a direct effect (i.e. the effect of treatment [A] on outcome [Y; A=0 versus A*=1]) and the natural indirect effect (NIE). There are two types of direct effect – a controlled direct effect (CDE) and a natural direct effect (NDE). The CDE is computed by holding the mediator to a constant. The NDE is computed by holding the mediator to the unexposed (control) level, allowing for natural variation. The CDE and NDE are equivalent unless there is an exposure-mediator interaction. The NIE

captures the effect of the mediation pathway (i.e. the average change in Y if the exposure is fixed to the level of the intervention and the mediator changes accordingly [i.e. A=0 to A*=1]; VanderWeele, 2015).

All analysis was done in Stata (version 15.0; StataCorp, 2017) in four steps. First, the data was screened using Little's test (command: *mcartest*), with the intention to use multiple imputation (command: *mice*) to manage missing values provided that missingness was independent of the unobserved and observed data.

Second, we compared baseline and 1-month follow-up values between the groups on variables for the analysis, with a 95% CI for the comparison of measures at 1-month follow-up because this was the level precision set for the primary outcome in the original trial.

Thirdly, univariate regression models were fitted to demonstrate significant associations between treatment and mediator; mediator and outcome; and treatment and outcome – each fitted univariably and multivariably to identify potential confounding. At baseline, the following participant measures were used as covariates: sex, age, months of regular cocaine use, months of general drug counselling and CEQ-F score.

Finally, the causal mediation analysis was done using the command *paramed* (Dunn et al., 2015). Paramed supports use of count-based outcome measurement (as used here), and gives standard errors (SE), confidence intervals (CI) and parameter estimates for the TE, CDE, NDE, and NIE by the delta method. Given the small sample size and exploratory nature of the analysis, these parameters were estimated by bootstrapping with 80% confidence intervals for hypothesis testing.

RESULTS

Participant enrolment and missing data

Fifty-eight patients were screened for the study of whom 35 were enrolled. As planned, 30 participants completed the assessment phase and were randomised to the control group (n=14) and the intervention group (n=16).

All participants completed the 1-month follow-up, except one member of the control group who declined to complete the DERS. All participants, bar one from each group, completed the 3-month follow-up. A non-significant Little's test statistic supported use of multiple imputation for the missing DERS total score (χ^2 [16] = 14.50; p = 0.561), and the two missing values on the NDA outcome (χ^2 [36] = 11.38; p = 1.000).

Baseline characteristics and group differences on emotion regulation and craving

There was good group balance on baseline characteristics (**Table 1**). The overall CEQ-F sample mean at baseline was 62.7 (SD 20.2). The CEQ-F had good internal reliability (Cronbach's alpha 0.83). The overall sample mean for the DERS at baseline was 103.3 (SD 26.29) with excellent internal reliability (alpha 0.93).

Table 2 shows the summary values on the variables for the causal mediation model at baseline and the two follow-ups, by group.

At baseline, there were no group differences on the measures of cocaine use, CEQ-F and DERS. Compared to the control group, participants in the intervention group had lower CEQ-F scores at 1-month follow-up (*g* = -1.62; 80% CI -0.80 to -2.45). The intervention was also associated with greater NDA at the 3-month follow-up (*g* = 0.38; 80% CI 0.30 to 1.28). There was complete concordance between self-report and UDS data (i.e. all participants who reported cocaine use in the past 7 days had a cocaine positive UDS, and all participants who reported no cocaine use in the past 7 days had a negative UDS; kappa = 1.00).

For the DERS, there was no statistically significant group difference at 1-month follow-up (*g* = -0.45; 80% CI -0.93 to 0.02).

Causal mediation analysis

Assumptions for Mediation

Univariate regression models were first fitted to each model pathway. Separate linear regression models tested the direct effect of treatment on the mediator (path a') to meet assumptions for mediation. The intervention was associated with lower scores on the CEQ-F at 1-month follow-up (F [1,28] = 20.99; adjusted R^2 = 0.408; p < 0.0001). However, the intervention was not associated with any meaningful change on the DERS (F [1,28] =1.63; adjusted R^2 = 0.021; p = 0.212).

To test the effect of the CEQ-F on 3-month NDA outcome, a Poisson regression model was fitted to the NDA outcome. Lower CEQ-F scores at 1-month were associated with greater cocaine abstinence (Likelihood Ratio [LR] X^2 [1] = 80.67; p<0.0001; Pseudo R^2 = 0.252). The intervention was also associated with increased NDA at three months (LR X^2 [1] = 21.16; p<0.0001; Pseudo R^2=0.066). Higher DERS score at 1-month was associated with less abstinence at 3-months (LR X^2 [1] = 27.73; p<0.0001; Pseudo R^2 = 0.087). However, since the DERS scores at 1-month were not associated with the intervention, it did not meet the minimum requirement for mediation and this variable was dropped from further analysis.

Identification of Covariates

Table 3 shows the results of univariable and covariate-adjusted regression models. The univariable models fitted indicated that months of regular cocaine use (p=0.035), baseline CEQ-F (p = 0.030) and trial group (p < 0.0001) were all univariable predictors of 1-month CEQ-F score. However, in the multivariable model only trial group was associated with CEQ-F score (adjusted R^2 0.479; p = 0.002).

Age (p = 0.001), months of regular cocaine use (p = 0.003), baseline CEQ-F (p < 0.0001), baseline cocaine use (p < 0.0001), and trial group (p < 0.0001) were all predictors of change on the outcome. Then, in an adjusted model (Pseudo R^2 0.201), sex (p = 0.043), baseline CEQ-F (p = 0.006), baseline cocaine use (p = 0.001), and trial group (p < 0.0001) were all associated with outcome.

Based on the adjusted models for 1-month craving and 3-month cocaine abstinence, sex, baseline CEQ and baseline cocaine use were included in the final model as potential confounders (**Table 4**). The model was run bootstrapped with 10,000 replications.

Mediation Analysis

Overall, there was a significant association of the intervention on NDA outcome (TE 1.499; 80% CI 1.114 to 1.970; p=0.012). With no evidence of an exposure-mediator interaction, the CDE and NDE are equivalent, and NDE is reported only herein.

There was no evidence of a significant direct effect (NDE = 0.855; 80% CI 0.569 to 1.175; p = 0.242) and a rate ratio coefficient close to 1 indicated little-to-no difference between participants receiving the intervention or control through the model's direct causal pathway. This was underscored by the Poisson model (Coefficient -0.156; 95% CI -0.419 to -0.106; p = 0.242). The mediating pathway was significant (NIE = 1.753; 80% CI 1.334 to 2.936; p < 0.0001) indicating that a reduction in craving at 1-month follow-up was associated with increased abstinence in the participants in the intervention group.

DISCUSSION

Using data from a randomised controlled trial, we present an exploratory mediation analysis providing preliminary evidence for a mediating effect of the frequency of intensity, imagery and intrusiveness aspects of cocaine craving (as measured by the CEQ-F) on cocaine abstinence among patients allocated to MFCT.

Both treatment allocation and craving were independently associated with cocaine use and after covariate adjustment, study data suggest a causal effect of MFCT on cocaine abstinence via reduced craving experience. The significant NIE from the causal mediation

model provides evidence in support of our hypothesised therapeutic change mechanism. In spite of the small sample, this was strong effect: once the effect of craving at one month was accounted for, the model showed no statistically significant direct effect of MFCT on outcome.

Based on this analysis, there was no support for the hypothesis that emotion regulation mediates cocaine abstinence after therapy. Reduced DERS scores were associated with the NDA outcome at 3-month follow-up, but this was an independent effect that was not linked to the intervention. However, it would be wrong to miss the opportunity to help patients in this area. Previous studies have suggested that individuals with CUD show stronger responses to emotional stimuli (Aguilar de Arcos, Verdejo-Garcia, Peralta-Ramirez, Sanchez-Barrera, & Perez-Garcia, 2005) and emotion regulation can improve as abstinence is sustained (Fox et al., 2007). It is possible that a lack of association between emotion regulation and treatment in our study may in part be because the DERS (and the CEQ-F) does not capture motivations to use drugs to change emotional state. During assessment and therapy sessions, participants collaboratively explored and addressed craving and cocaine use as a response to positive and negative mood. Substance use as a strategy for coping with negative affect (and associated craving) is likely to play an important role in use and relapse and may be a more relevant predictor than the general aspects of emotion regulation addressed in the DERS.

The present analysis supports assessing and targeting craving experience to inform psychological treatment of CUD (Marsden et al., 2014). While it is not currently feasible to directly target sub-threshold, cue-induced responses, MFCT targets cognitive and affective elaborations with the aim of diminishing the strength of future craving experiences. By capitalising on the malleability of memory reconsolidation processes, our novel psychotherapy appears to reduce drug approach cognitions and responses to cocaine conditional cues so that subsequent craving experiences are better controlled (Kavanagh et al., 2005). Better cognitive control is likely to increase self-efficacy when exposed to high-risk situations (Sklar, Annis, & Turner, 1999), and may lead to reductions in activity in reward regions in the brain (Volkow et al., 2010).

Nevertheless, as we have noted, craving does not always precede cocaine use. Some people with CUD, find that cocaine seeking has become highly automatized and if there is immediate drug access, there may be minimal, if any, craving and cognitive elaboration. Our efforts to help patients become aware of automatic processes may provide some protection to enable a process of reflection and alternate action.

In the context of the wider literature there is mixed evidence on the role of craving in predicting cocaine use and a number of studies have concluded that craving does not reliably predict cocaine use (Miller & Gold, 1994; Weiss, Griffin, & Hufford, 1995). However, more recent studies favour craving as a predictor of cocaine-seeking (Da Silveira, Doering-Silveira, Niel, & Jorge, 2006; Preston et al., 2009) and relapse (Crits-Christoph et al., 2007; Paliwal, Hyman, & Sinha, 2008; Rohsenow, Martin, Eaton, & Monti, 2007; Sinha, Garcia, Paliwal, Kreek, & Rounsaville, 2006; Weiss et al., 2003). The present study contributes to and extends this mixed extant literature showing craving as measured by the CEQ-F as a strong predictor of cocaine use.

It is important to note that memory reconsolidation interventions are at a relatively early stage of development (Exton-McGuinness & Milton, 2018; Monfils & Holmes, 2018). However, the literature is growing with encouraging findings from psychological laboratory studies with users of nicotine, heroin, alcohol and cocaine (Germeroth et al., 2017; Hon, Das, & Kamboj, 2016; Xue et al., 2012) and pharmacological interventions (e.g. propranolol; Lonergan et al., 2016; Saladin et al., 2013; Xue et al., 2017). Taken together, these interventions suggest that memory-reconsolidation techniques can reduce craving and subsquent drug-seeking. To our knowledge, our study is the first to apply memory reconsolidation approaches in the addiction clinic setting. Replication studies by other groups are now warranted.

Study strengths include the experimental design and control over confounding, along with the pre-planned analysis plan, and a counterfactual framework analysis of causal mediation. We also acknowledge several limitations. Although in-line with recommendations for pilot studies, this was a small sample study and the results must be regarded as exploratory and in need of replication. A longer follow-up period up to 12 months is recommended to examine the robustness of MFCT-based cocaine abstinence against time, given the relapsing nature of CUD. Nevertheless, the present findings are encouraging and give impetus for future superiority randomised controlled trials of MFCT alongside general counselling for people with primary CUD, and as an adjunctive intervention for patients with concurrent CUD and opiate use disorder (Marsden et al. 2019).

At present, CUD is a significant and hard to treat public health problem with limited treatment options and it is crucial to understand the mechanisms underlying potential new treatments. This study positions craving as an important mediator in reducing cocaine use in participants receiving MFCT.

CONFLICTS OF INTEREST

The authors declare that they have no financial investment or relationship with any organisation that could inappropriately influence or benefit this research.

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J.M. is a clinical research and practitioner psychologist (licensed with the British Association of Behavioural and Cognitive Psychotherapies). In the past three years, he declares grant support from Indivior (via Action on Addiction) for a study of adjunctive psychosocial intervention during opioid agonist treatment (ARC Trial; 2015-2019); NIHR (HTA) for a trial of extended-release naltrexone (NEAT trial; 2016-2018); and Indivior for a trial of extended-release buprenorphine maintenance (EXPO trial; 2019-2021). J.M. acknowledges part-time employment as Senior Academic Advisor for the Alcohol, Drugs and Tobacco Division, Health Improvement, Public Health England and is a consultant for the Centre for Clinical Trials Network at the US National Institute on Drug Abuse. In the past three years, he has received honoraria Martindale (2017; expert meeting on opioid use disorder); and Indivior (via PCM Scientific) for chairing (2016-2017) for the conference on Improving Outcomes in Treatment of Opioid Dependence. He holds no stocks in any company.

L.M. declares grant funding for an investigator-led, educational grant from Indivior (administered by Action-on-Addiction) for the ARC Trial. He holds no stocks in any company.

J.S. is a researcher and clinician who has worked with a range of types of treatment and rehabilitation service-providers. He is supported by the NIHR BRC for Mental Health at SLaM and KCL. He has also worked with a range of governmental and non-governmental organisations, and with pharmaceutical companies to seek to identify new or improved treatments from whom he and his employer (KCL) have received honoraria, travel costs and/or consultancy payments. This includes work with, during past 3 years, Martindale, Reckitt-Benckiser/Indivior, MundiPharma, Braeburn/Camrus (none of these activities relate to the study being reported here).

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All other authors declare no competing interests.

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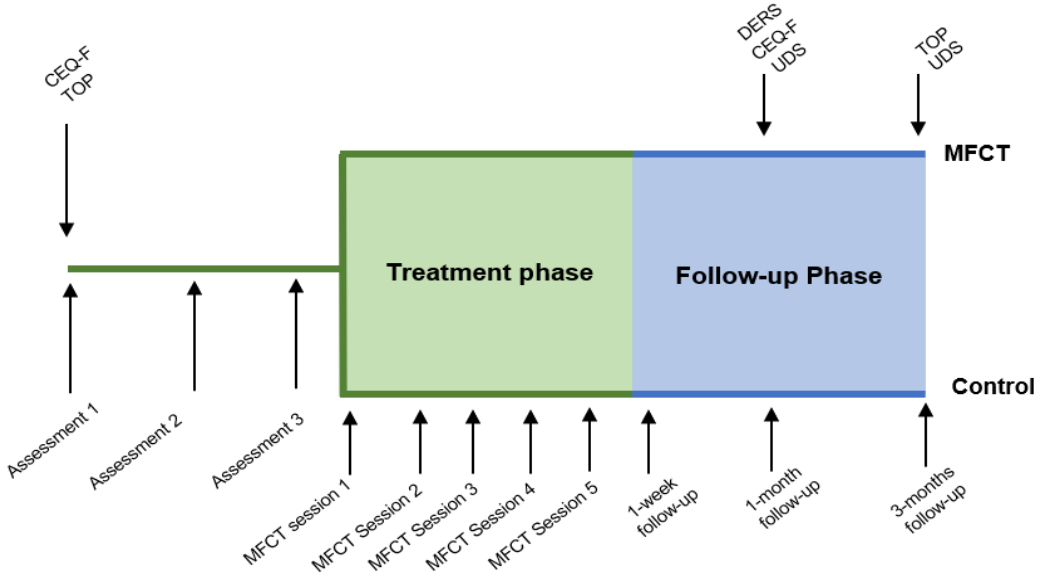
Figure 1: Timing of Study Measures



Note:

CEQ, Craving Experience Questionnaire;

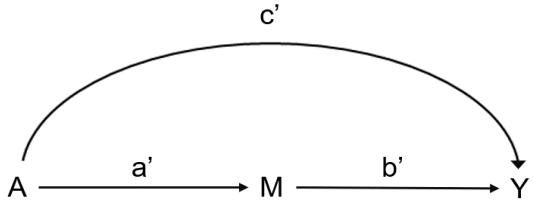
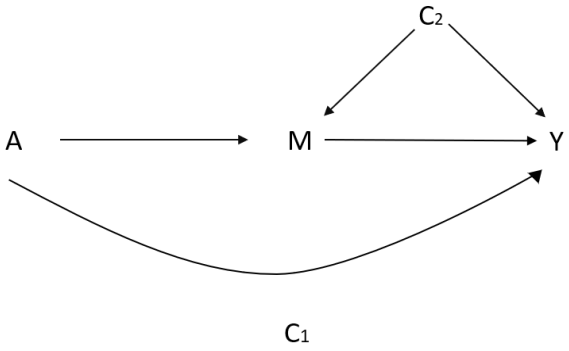
DERS, Difficulties in Emotion Regulation Scale;

MFCT, Memory-focused Cognitive Therapy;

UDS, Urine Drug Screen;

TOP, Treatment Outcome Profile (time-line follow-back interview for past 28 days).

Figure 2. Baron and Kenny mediation model and counterfactual framework

1 Baron and Kenny model	**2** Counterfactual framework
 A = exposure, M = mediator, Y = outcome	 A = exposure, M= Mediator, Y = outcome; C1 = exposure-outcome confounder, C2 = mediator-outcome confounder
Regression model notation: 1) $E(Y\|A=a) = \beta 0 + \beta 1a + e$ 2) $E(M\|A=a) = \beta 0 + \beta 1a + e$ 3) $E(Y\|M=m\ A=a)\ \beta 0 + \beta 1M + e$ 4) $E(Y\|A=a) = \beta 0 + \beta 1X + \beta 2M + e$	Regression model notation: $RR^{CDE}(m) = \exp\{(\theta_1+\theta_{3m})(a-a^*)$ $RR^{NDE} = \exp\{(\theta_1+\theta_3\beta_0+\theta_3\beta_{1a^*}+\theta_3\beta'_2c+\theta_3\theta_{2\sigma}^2)(a-a^*)$ $+0.5\,\theta_3^2{}_\sigma^2(a^2-a^{*2})\}$ $RR^{NIE} = \exp\{(\theta_2\beta_1+\theta_3\beta_{1a})(a-a^*)$

Note:

A, exposure (intervention or control group by random allocation);

M, mediator (CEQ-F and DERS at 1-month post-intervention follow-up);

Y, outcome (Number of Abstinent Days [NDA] at 3-month follow-up);

RR, rate ratio (continuous mediator and Poisson regression given count-based outcome)

CDE, controlled direct effect;

NDE, natural direct effect;

NIE, natural indirect effect.

Table 1. Participant characteristics at baseline

Variable	**Control** (n=14)	**Intervention** (n=16)
Male	9 (64%)	11 (69%)
Age, years	45.0 (6.5)	43.3 (6.7)
Months of regular cocaine use (IQR)	108.0 (69-150)	94.5 (60-120)
Months in treatment at enrolment (IQR)	5.0 (1.0, 25.5)	8.5 (2.5, 53.5)
DSM5 CUD diagnosis (severity):		
Moderate (4-5 symptoms)	4 (29%)	3 (19%)
Severe (6-11 symptoms)	10 (71%)	13 (81%)
Medication for co-occurring opioid use disorder:		
Oral methadone (mg/day)	5 (55.0)	6 (61.7)
Sublingual buprenorphine (mg/day)	4 (13.0)	5 (14.4)

Note:

Data are number of participants, mean (SD) or median (IQR, inter-quartile range)

Table 2. Variables included in analysis at baseline, one-month follow-up (potential mediators) and outcome at 3-month follow-up, by study group (n=30)

Point/variable	**Control** (n=14)	**Intervention** (n=16)	**Difference (95% CI)**	**Effect size (CI)** [d]
Baseline	M (SD)	M (SD)		
Cocaine NDA [a]	46.43 (27.98)	45.09 (16.64)	-1.34 (-18.30 to 15.62)	-0.06 (-0.78 to 0.66)
CEQ-F [b]	67.5 (17.00)	58.5 (22.40)	-9.00 (-24.05 to 6.05)	-0.44 (-1.16 to 0.29)
DERS [c]	104.71 (22.28)	102.06 (30.05)	-2.65 (-17.38 to 22.68)	-0.10 (-0.81 to 0.62)
1-month follow-up				
CEQ-F	51.75 (22.72)	14.77 (21.47)	-36.98 (-53.51 to -20.45)	-1.62 (-0.80 to -2.45) †
DERS	98.21 (22.67)	85.50 (30.58)	12.71 (-7.67 to 33.10)	-0.45 (-0.93 to 0.02) ‡
3-month follow-up				
Cocaine NDA	51.55 (35.34)	77.07 (27.50)	25.52 (10.44 to 40.59)	0.38 (0.30 to 1.28) ‡

Note:

M, mean; SD, standard deviation; CI, confidence interval;

[a] NDA, number of days abstinent from cocaine past 28 days;
[b] CEQ-F, Craving Experience Questionnaire (frequency version); recall period: past 2 weeks (total score, range: 0-110);
[c] DERS, Difficulties in Emotion Regulation Scale; recall period past two weeks (total score, range: 36-180);
[d] Hedge's *g*;
† Effect size CI advanced specified at 95% CI;
‡ Effect size CI advanced specified at 80% CI.

Table 3. Unadjusted and covariate adjusted causal mediation analysis of treatment exposure on cocaine craving and cocaine use outcome at 3-month follow-up.

Variable/path to mediator	**Coef.**	**95% CI**	***SE***	***t***	**P-value**
Unadjusted					
Sex	3.455	-19.652 to 26.561	11.280	0.31	0.762
Age	1.099	-0.533 to 2.730	0.797	1.38	0.179
Months in general counselling	-16.182	-37.085 to 4.722	10.205	-1.59	0.124
Months regular cocaine use	21.970	1.661 to 42.280	9.915	2.22	0.035
Baseline CEQ-F [a]	0.560	0.057 to 1.064	0.246	2.28	0.030
Baseline cocaine use	-0.989	-2.748 to 0.771	0.859	-1.15	0.259
Group	-36.981	-53.515 to -20.446	8.072	-4.58	<0.0001
Model (R^2 0.605; adj. R^2 0.479)					
Sex	1.532	-17.455 to 20.519	9.155	0.17	0.869
Age	0.315	-1.000 to 1.630	0.634	0.50	0.624
Months in general counselling	-11.660	-28.403 to 5.083	0.163	-1.44	0.163
Months regular cocaine use	12.645	-6.204 to 31.495	0.178	1.39	0.178
Baseline CEQ-F [a]	0.278	-0.181 to 0.738	0.221	1.26	0.222
Baseline cocaine use	-0.493	-2.076 to 1.090	0.763	-0.65	0.525
Group	-29.290	-46.775 to -11.806	8.431	-3.47	0.002
Variable/paths to outcome	**IRR**	**95% CI**	***SE***	***z***	**P-value**
Unadjusted					
Sex	1.199	0.997 to 1.441	0.112	1.93	0.053
Age	0.979	0.967 to 0.992	0.006	-3.22	0.001
Months in general counselling	1.000	0.997 to 1.004	0.002	0.23	0.821
Months regular cocaine use	0.773	0.654 to 0.914	0.066	-3.01	0.003
Baseline CEQ-F [a]	-0.990	-0.986 to -0.994	0.002	-5.10	<0.0001
Baseline cocaine use	1.038	1.023 to 1.053	0.007	5.17	<0.0001
CEQ-F at 1-month (mediator)	0.984	0.981 to 0.988	0.002	-8.39	<0.0001
Group	1.494	0.1256 to 1.779	0.132	4.53	<0.0001
Model (Pseudo R^2 0.201)					
Sex	1.238	1.007 to 1.522	0.131	2.02	0.043
Age	0.995	0.982 to 1.009	0.007	-0.73	0.466
Months in general counselling	1.007	0.840 to 1.209	0.094	0.08	0.937
Months regular cocaine use	0.904	0.748 to 1.091	0.087	-1.05	0.292
Baseline CEQ-F [a]	0.994	0.989 to 0.998	0.002	-2.74	0.006
Baseline cocaine use	1.030	1.012 to 1.049	0.009	0.006	0.001
Group	1.420	1.168 to 1.726	0.141	0.001	<0.0001

Note:

[a] CEQ-F, Craving Experience Questionnaire (frequency version); recall period: past 2 weeks (total score, range: 0-110);

Table 4. **Causal mediation model, adjusted for covariates**

Estimates (Poisson model)	**Coef.**	**95% CI**	**SE**	**P-value**
Model (Pseudo R^2 0.325)				
Sex	0.200	0.008 to 0.392	0.099	0.041
Baseline cocaine use	0.021	-0.004 to 0.039	0.010	0.018
Baseline CEQ-F score	-0.004	-0.008 to 0.001	0.002	0.093
CEQ-F (mediator)	-0.016	-0.021 to -0.011	0.004	<0.0001
Group	-0.156	-0.419 to 0.106	0.134	0.242
Summary of effects	**Coef.**	**80% CI**	**SE ***	**P-value**
NDE	0.855	0.569 to 1.175	0.240	0.242
NIE	1.753	1.334 to 2.936	0.875	<0.0001
Total effect	1.499	1.114 to 1.970	0.356	0.012

Note:

NDE, Natural direct effect; equivalent to CDE without mediator-outcome interaction

NIE, Natural indirect effect;

* Bootstrapped

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